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# (54) Pharmaceutical products for promoting wound healing

(57) Pharmaceutical products for promoting wound healing comprise a carrier for covering wounds and injuries having an H-1 and/or H-2 receptor-blocking antihistamine as active ingredient e.g. cimetidine or ranitidine and, if desired, other pharmaceutically acceptable additives.

The product is prepared by treating a solid, suitably porous, carrier with a solution containing 0.1 to 50% by weight of the active ingredient.

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# PHARMACEUTICAL PRODUCTS FOR PROMOTING WOUND HEALING

The present invention relates to pharmaceutical products for use in the treatment of wounds and injuries.

Wound care, after accidental injury, burning or surgery, represents a fundamental part of curing.

For a long time, the treatment of wounds has been limited to the following operations:

- mechanical purification of the wound (which, technically, can never be complete in any case);
- treatment with disinfectants; and
- mechanical protection of the wound (dressing).

However, wound healing is still a lengthy process even when the above operations are performed in a skilled manner.

Treatment is most successful when the requirements influencing wound healing are simultaneously satisfied.

The most important external and internal factors of wound healing are as follows:

- the normal metabolism of the surrounding tissues (adequate blood supply and oxygenation);
- keeping the wound clean (the removal of pus and decomposed tissue residue); and
- prevention or elimination of microbial contamination.

The various wound-treating methods known at present take these factors into consideration; however, they are usually capable of satisfying only one factor without any influence on the others; in some cases, there is even an adverse effect, for example, infection of the wound is prevented, but oxygenation is inhibited by using antibiotic ointments.

A prime condition of successful wound healing is the adequate respiration of the wound. A number of ways have been found to achieve this purpose, a common characteristic of which consists in the use of a porous layer, useful for covering the wound. This porous layer may be a simple textile with a loose network (e.g. cotton, cloth, gauze, mull), synthetic or natural porous matrices, or combinations thereof, impregnated with other materials, such as disinfecting and preserving agents, or the like, which promote wound healing. In this connection, examples of materials are as follows: a

plaster consisting of a copolymer of acrylic acid and acrylate ester (South African Patent Specification No. 68/1631); a film of similar composition (United States Patent Specification No. 3,932,602); a cotton textile impregnated with cellulose acetate (French Patent Specification No. 4656 M); and silicone polymers or synthetic as well as native rubber-based matrices (United States Patent Specifications No's. 4,336,243 and 4,307,717).

In the area of traditional wound-treatment, the discovery of swellable cross-linked polysaccharide-type polymers as wound-dusting powders represented an important break through (British Patent Secification No. 4,454,055). Owing to strong absorption of liquids, the spherical particles, usually of about 100 to 300 µm in diameter, when spread in a dry state onto the surface of the wound, not only dry the oozing wound but also take up the pus, tissue residues and bacteria together with the liquid and, thus, purify the wound in a much more effective manner than may be achieved by the use of any purely mechanical method (United States Patent Specification No. 4,225,580).

Continued research, aimed at increasing the wound-curing effect of hygroscopic polymers, led to other additives, such as disinfecting agents, for example,

polyvinylpyrrolidone - iodine complex (British Patent Specification No. 2,099,704), or silver-sulfadiazine (Symp. Ser. 256, 181, (1984), 7) being applied to the cross-linked grains or lamellae used as carriers.

The above treatments characteristically satisfy the external conditions of wound healing.

Further progress was achieved with the recognition that appropriate levels of calcium and potassium ions play important roles both in and around the wound. In FRG Patent Specification No. 3,416,777, a process is described, wherein the internal requirements of wound healing are also partially considered, the concentration of calcium and potassium ions being increased to the desired level by the use of compositions containing solutions of calcium and potassium salts.

The present invention provides pharmaceutical compositions which satisfy simultaneously and optionally both the external and internal conditions of wound healing and comprise anti-inflammatory, epithelising H-1 and/or H-2 receptor-blocking antihistamines (e.g. cimetidine or ranitidine) together with a suitable carrier for covering the wound.

Thus, in a first aspect of the present invention, there is provided a pharmaceutical product for promoting wound healing comprising at least one H-1 and/or H-2 blocker as active ingredient on a carrier suitable for covering wounds.

By an H-1 and/or H-2 "blocker" is meant an H-1 and/or H-2 receptor-blocker.

The term "wound" as used herein refers to any part of the human or animal body suitable for treatment with the products of the invention, such as wounds, open sores, ulcers etc.

The wound healing promoting activity of H-2 receptor-blocking agents can be explained by reference to the pathological progress of ulcers or other wounds which heal with difficulty. Three phases are distinguishable in the development of an ulcer disease, essentially starting with a chronic inflammation process characterised as follows:

- the amine phase (mediated by histamine and $H^+$-substances);
- the quinine phase (mediated by bradykinin); and
- the PG phase (mediated by various prostaglandin fractions which are responsible for the inflammation).

The first phase of the continually recurring process, that is, the enlargement and deepening of wounds, can be prevented by the topical use of H-2 receptor-blocking agents. Wound healing is considerably shortened due to the absence of the second and third phases of chronic inflammation. Thus, the practical importance of the H-2 receptor-blockers lies in their ability to assure the rapid and untroubled healing of wounds, by preventing the development of secondary syptoms and, thus, avoiding frequently lengthy treatment.

H-1 receptor-blocking agents, for example, dimethindene maleate, tripelenamine and phenindamine, diminish the permeability of the capillaries and inhibit the action of hyaluronidase, thus moderating serous inflammation.

Any suitable carrier may be used, but it will be appreciated that it is desirable to provide a carrier which is capable of extensively meeting external conditions of wound healing, whilst ensuring that healthy cells surrounding the wound are not superfluously saturated by active ingredient.

The carrier may be, for example, liquid, ointment-like or solid. Preferred are solid carriers, which are simultaneously capable of purifying the wound and preventing oedema due to their hygroscopic properties.

Particularly preferred are swellable, cross-linked, polysaccharide-type, hydrophilic polymers (such as dextran or cyclodextrin grain polymers cross-linked with epichlorhydrin); however, other carriers possessing hygroscopic properties and a porous structure allowing the wound to breathe are also suitable.

The products of the present invention may comprise mixtures of H-1 and H-2 blockers, or just H-1 blockers or H-2 blockers, preferably H-2 blockers and, most preferably, just cimetidine or ranitidine.

Good results have been achieved using a hygroscopic, sponge foam-based wound-covering sheet or gauze containing cimetidine.

In an alternative aspect, the present invention provides a process wherein a suitably porous, hygroscopic carrier for covering a wound is treated with a solution containing a H-1 or H-2 receptor-blocking antihistamine as active ingredient, and which is subsequently, if desired, dried and sterilized.

H-2 blockers are suitably provided in the form of a 0.1 to 50%, preferably 0.1 to 30% by weight aqueous or ethanolic solution. Cimetidine is preferred, but other H-2 blockers exerting a cyto-protective effect, such as ranitidine, famotidine, burinamide or metiamide, may be used.

According to a preferred embodiment of the present invention, the wound-curing product is prepared from a hydrophilic polymer grain useful as a wound-dusting powder, such as a dextran grain polymer cross-linked with epichlorhydrin, by soaking with an aqueous or ethanolic solution containing 0.1 to 10% by weight of cimetidine to swell the grains, then drying at a temperature of below 5°C and sterilizing.

We have found that, in wound-dusting powders prepared as above, the mixture of carrier and active ingredient is synergistic, thus reducing the period of wound healing by as much as several days.

Other hydrophilic polymers such a cellulose derivatives, alginates, cyclodextrin or the like may also be used as carriers for the wound-dusting powders of the invention.

The solid carrier may also be built up in such a way that the polymeric particles swollen in the solution of the active ingredient are applied in a wet state onto a gauze and dried until reaching a defined moisture content; or a polyurethane sheet, useful for covering the wound, is soaked in a solution contining 5.0 to 50.0% of active ingredient in such a manner that the sheet contains 10 to 200 mg/dm$^2$ of active ingredient, followed by drying and being cut into pieces of appropriate size.

If desired, the product may also be formulated as a gel. In this case an acrylic acid polymer may be used which is swollen in a solution containing for example, methyl-4-hydroxybenzoate, then gelled by the use of 5.0 to 30.0% by weight of sodium hydroxide solution with stirring, followed by addition of the solution containing the active ingredient and, after homogenizing, optionally being packaged into tubes.

The products of the invention may be supplemented by pharmaceutically acceptable additives, especially those such as water-soluble or fat-soluble chlorophyll or hexachlorophen which possess advantageous properties for wound healing.

The invention is illustrated in detail by the following non-limiting Examples.

Example 1

Dextran grain polymer cross-linked with epichlorhydrin (1000g, grain size 120 to 320 µm) are swollen in 600 ml of an aqueous solution containing 12g of cimetidine and adjusted to pH 2 with hydrochloric acid. The polymer, swollen to 3 to 4 times its original volume, is filtered off, re-suspended in 300 ml of 0.01 M sodium hydroxide solution, filtered off again and then dehydrated with 500 ml of ethanol. The ethanol

treatment is repeated twice. The dehydrated product is subsequently dried below 50°C and packaged in spraying boxes. Sterilization is effected using $^{60}Co$ isotope with a radiation dose of 20 kGy, or with freon gas.

The resulting product contains 0.15 to 0.2% by weight of cimetidine.

Example 2

Dextran grain polymer cross-linked with epichlorhydrin (1000g, grain size 120 to 320 µm) is moistened with 100 ml of 96% ethanol, then uniformly soaked with a solution of 10g of dimethindene maleate in 250 ml of 96% ethanol. The wet aggregate of grains is dried at a temperature below 50°C such that drying loss does not exceed 8% by weight. The product is packaged in spraying boxes and sterilized using $^{60}Co$ isotope with a radiation dose of 20 kGy.

The product obtained contains 0.92% by weight of dimethindene maleate.

Example 3

Dextran grain polymer cross-linked with epichlorhydrin (1000g, grain size 40 to 120 µm) is moistened with 100 ml of 96% ethanol, then uniformly soaked with a solution of 20g of thenalidine in 300 ml of 86% ethanol. The wet aggregation of grains is dried at a temperature below 50°C such that drying loss does not exceed 8% by weight. The dried grain aggregate is put into a paper filter-bag, then sealed between aluminum foils and sterilized as described in Example 1.

The product obtained contains 1.85% by weight of thenalidine.

Example 4

Dextran grain polymer cross-linked with epichlorhydrin (1000g, grain size 120 to 320 µm) is moistened with 100 ml of 96% ethanol, then uniformly soaked with a solution containing 5g of ranitidine in 200 ml of 96% ethanol. The wet aggregate of grains is dried at a temperature below 25°C such that drying loss does not exceed 8% by weight. The product is packaged in spraying boxes and sterilized as described in Example 2, or the whole operation carried out under aseptic conditions.

The product obtained contains 0.4% by weight of ranitidine.

Example 5

The process described in Example 4 is followed using a dextran grain polymer cross-linked with epichlorhydrin (grain size 40 to 120 µm). The dried product is put into paper filter-bags and then sealed between sheets of aluminum foil. The product is sterilized by irradiation or the whole operation is carried out under aseptic conditions.

Example 6

A polyurethane foam sponge sheet, suitable for wound covering, is soaked in a 5% by weight solution of cimetidine in 96% ethanol. The sheets are dried at a temperature below 40°C and then cut into pieces of the desired size. Sterilization is carried out by irradiation or by using ethylene oxide; or the whole operation is performed under aseptic conditions.

The product obtained contains 25 $mg/dm^2$ of cimetidine.

Example 7

A sheet of grey plain cotton cloth is soaked in a solution containing 10% by weight of cimetidine as described in Example 6, then cut into pieces of the desired size and an adhesive plaster is prepared which is useful for a rapid dressing.

The product obtained contains 50 mg/dm$^2$ of cimetidine.

Example 8

Acrylic acid polymer (5g) is swollen under germ-poor conditions in 500g of sterile distilled water cotaining 1.5g of methyl-4-hydroxybenzoate and, after adding 5g of 30% by weight sodium hydroxide solution, is stirred until a uniform gel is obtained. To the gel obtained, 1g of cimetidine hydrochloride, dissolved in 300g of sterile distilled water, is added, and the gel made up to 1000g with sterile distilled water. The product is packaged in tubes in a known manner.

The product obtained contains 0.1% by weight of cimetidine.

Example 9

Water-soluble chlorophyll (1g) is homogenized with 998g of a dextran grain polymer cross-linked with epichlorhydrin (grain size 120 to 320 µm). To the homogenate, a solution containing 5g of cimetidine in 200 ml of 96% ethanol is added, and the mixture stirred at room temperature for 2 hours. The product is dried at a temperature below 60°C with stirring. The dried product is packaged in spraying boxes and sterilized with a 20 kGy dose of gamma-radiation.

The product obtained contains 0.5% by weight of cimetidine.

Example 10

Fat-soluble chlorophyll (2.5g) is homogenized in a melt containing 268.5g of Macrogol 400, 20g of Macrogol 1540 and 29g of Polysorbate 80. The melt is cooled to 30°C and 660g of a dextran grain polymer cross-linked with epichlorhydrin (grain size 40 to 120 µm) and saturated with 20g of cimetidine (as described in Example 1), stirred in.

The paste obtained is suitably filled in 10g portions into polyethylene-mounted aluminum foil bags and sterilized using a 20 kGy dose of gamma-radiation.

The product obtained contains 1.98% by weight of cimetidine.

CLAIMS

1. A pharmaceutical product for promoting wound healing comprising at least one H-1 and/or H-2 blocker as active ingredient on a carrier suitable for covering wounds.

2. A product according to claim 1 wherein the carrier is a solid.

3. A product according to claim 1 or 2 wherein the carrier is porous.

4. A product according to any preceding claim wherein the carrier is hygroscopic.

5. A product according to any preceding claim wherein the carrier is an hydrophilic polymer.

6. A product according to claim 5 wherein the carrrier is a cellulose derivative, an alginate, a cyclodextrin or an acrylate.

7. A product according to claim 2 wherein the carrier is a cross-linked, polysaccharide-type polymer.

8. A product according to claim 7 wherein the carrier is a dextran or cyclodextrin grain polymer.

9. A product according to claim 8 wherein the polymer is cross-linked by epichlorhydrin.

10. A product according to any of claims 1 to 5 wherein the carrier is polyurethane foam or cotton cloth.

11. A product according to any preceding claim wherein the active ingredient is cimetidine, ranitidine, famotidine, burinamide, metiamide, dimethindene maleate, tripelenamine, phenindamine and/or thenalidine.

12. A product according to claim 11 wherein the active ingredient is cimetidine or ranitidine.

13. A product according to any preceding claim wherein the carrier is substantially saturated with active ingredient.

14. A product according to any preceding claim comprising 0.1-15% w/w of active ingredient.

15. A product according to claim 14 comprising 0.1-5% w/w of active ingredient.

16. A product according to any preceding claim comprising 10-200mg active ingredient per $dm^2$ of carrier.

17. A product according to any preceding claim further comprising one or more other pharmaceutically acceptable additives.

18. A product according to any preceding claim in the form of wound-dusting powder.

19. A product according to any of claims 1 to 17 in the form of a bandage or plaster.

20. A product according to any preceding claim for use in promoting wound healing.

21. The use of at least one H-1 and/or H-2 blocker in the preparation of a product as described in any of claims 1 to 19 for the treatment of wounds.

22. A process for the preparation of a product as described in any of claims 1 to 20 comprising treating the carrier with a solution containing 0.1 to 30% w/w of active ingredient.

23. A process according to claim 22 wherein the solution contains 0.3 to 10% of active ingredient.

24. A process according to claim 22 or 23 wherein the carrier is a hydrophilic polymer which swells on contact with the solution of active ingredient.

25. A process according to claim 22 or 23 wherein the carrier is polyurethane foam or cottom cloth and the solution contains 5 to 10% w/w of active ingredient.

26. A process according to claim 22 or 23 wherein the carrier is polyurethane foam or cotton cloth and treatment is with 10-200 mg active ingredient per $dm^2$ of carrier.

27. A pharmaceutical composition for promoting wound healing comprising 0.1 to 15% by weight of an H-1 and/or an H-2 receptor-blocking antihistamine as active ingredient on a solid, porous carrier suitable for covering wounds and injuries.

28. A process for the preparation of pharmaceutical compositions for promoting wound healing wherein a solid, porous carrier, suitable for covering wounds and injuries, along with, if desired, one or more other pharmaceutically acceptable additives, is treated with a solution containing 0.1 to 30% by weight of at least one H-1 and/or H-2 receptor-blocking antihistamine.

29. A product according to claim 1 substantially as described herein, with particular reference to the Examples.

30. A process according to claim 20 substantially as described herein, with particular reference to the Examples.

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